IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application	
Inventor: R. Christopher deCharms	Examiner: Ruth S. Smith
Application No.: 10/066,004	Art Unit: 3737
Filed: January 30, 2002	Confirmation No.: 7144
Title: METHODS FOR PHYSIOLOGICAL MONITORING, TRAINING, EXERCISE AND REGULATION	Customer No.: 021971

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, John Gabrieli, Ph.D., hereby declare, based on information and belief:

I currently serve as Grover Hermann Professor in Health Sciences and Technology and Cognitive Neuroscience at MIT, and as Director of the Martinos Imaging Center at the McGovern Institute, MIT. I have led a group working in the use of fMRI to study cognitive tasks since the early 1990's. My group has published papers in the field of fMRI since 1996, when I was an associate professor at Stanford. I hold a Ph.D. in Behavioral Neuroscience from the Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology.

I have been asked by Christopher DeCharms of Omneuron to comment on several issues in relation to his patent application, directed to using fMRI for guiding the cognitive tasks of subjects and for cognitive training. I am familiar with what is claimed, and with the field of fMRI and

cognitive control both now and at the time that this application was filed. I have no financial interest in Omneuron.

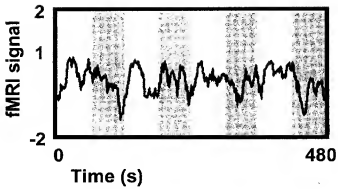
It is my opinion that at the time this application was originally filed, January 30, 2001, the invention described would not have been obvious to a person "of ordinary skill in the art" of fMRI. I was knowledgeable in fMRI and cognitive training and related areas at that time, as were many researchers in my group. In my opinion, it was not at all clear at the time whether or not one could successfully use fMRI to guide cognitive processes in a subject, e.g., training subjects to use the fMRI activity measurements to alter fMRI activity and guiding cognitive tasks of subjects. I believe this for the following reasons:

First, it was not obvious that if one wanted to guide the cognitive process of a subject, one should present a subject with information derived specifically from a localized region of the brain (i.e., to use "region-of-interest" ("ROI") analysis), rather than presenting the subject with statistical maps or other volumetric analysis methods. It is possible to measure fMRI signals in a large variety of ways. I am not aware of any suggestion in the prior literature that would direct one to use ROI analysis to guide cognitive processes in a subject.

Using information from a localized region of the brain is a method commonly referred to as in the field as "ROI analysis." Most of the limited use of fMRI up to 2001 had focused on how quickly one could generate a statistical map using volumetric analysis, i.e., how quickly it was possible to produce a statistical map of activation. For example, a frequent clinical use of fMRI up untill that time had been mapping of brain areas involved in language tasks. In one example, investigators showed that the statistical map of areas involved in language showed gradual improvements in statistical quality as the data were gathered over a few minutes, which could be useful for planning a surgical procedure. However, the scientists watching the fMRI data were ultimately watching statistical images showing the whole brain, not time-course data averaged from a localized region, which ultimately proved to be the successful method for guiding cognitive tasks.

Second, it was not at the time clear whether the fMRI signal from a single individual measured without averaging over repeated trials would contain information suitable for guiding the cognitive tasks of the subject, or for training. The signal from fMRI during a scanning session in trials from individual subjects is very noisy and is normally averaged over many trials and typically over many subjects. Most studies at the time would have subjects perform a task like tapping their finger or looking at an image repeatedly (e.g., 10 times), and then collect data from a large number of subjects (e.g., 12), and then average the results to produce a map of which brain areas are activated using specialized software. This is one kind of work that my lab specializes in. At the time, our group had measured brain activation in both healthy subjects performing cognitive tasks, and in patients with neurological or psychiatric diseases. Normally, these kind of experiments involve using specialized software like Statistical Parametric Mapping (SPM) designed for averaging fMRI activity over many repetitions of a task from each subject (the experiment design matrix), multiplying this by a hemodynamic response function, and then again averaging the single subject averages over many subjects in order to compute a general linear model or determine which brain areas are correlated with a task or disease (i.e., using fixed effects and/or random effects statistical mapping methods). When successful, this can produce correlation maps of which areas of the brain are involved in conducting a task, or involved with a disease.

The fact that it is possible to make correlation maps on average data, particularly from groups, does not make it at all obvious that one could use fMRI information from a single individual without averaging over repeated trials to try to guide the cognitive processes of that individual. This is illustrated below:



The figure herein shows the actual rtfMRI signal originating from the brain of a single subject on a single trial, measured by Dr. deCharms for a paper the Dr. deCharms and I published together. This figure shows the timecourse of fMRI activation measured each second over four minutes from a region of interest in the somatomotor cortex in a single subject, prior to rtfMRI-based training. During periods shown with the heavy black bars, the subject was instructed to try to increase the activation measured from the target region of interest. As one can see, this signal is noisy: The signal from times of increased activation are difficult to distinguish from the signal from lower activitation. It was not at all clear that a subject would be able to use information like this to guide their cognitive processes. In technical terms, it was not obvious that the signal-to-noise ratio and contrast-to-noise ratio of this type of data would be adequate to meaningfully guide the cognitive process of a subject. It was entirely possible that the data would be so "noisy" that attempting to guide the cognitive tasks of a subject or to train a subject using this data would fail to have any meaningful utility.

Third, while investigators had assigned many types of tasks to a subject inside a scanner for investigation of brain activity during the performance of these tasks, it was not obvious that one could "close the feedback loop" and actually successfully use the fMRI information derived from the brain itself *as the basis for guiding the cognitive processes of the subject.*

There were multiple tools available for guiding subject behavior inside a scanner. The software package E-prime is one example that had been used for this purpose, and "Psych Toolbox" was another. Our group has used both. Some groups had also measured brain activation in real time. In fact, the idea was around that one could measure the brain activation in real time to monitor the progress of the experiment, and make sure that it was working adequately (i.e., make sure that the scanner was working properly, and that data were adequate, and that the subject wasn't moving too much). Voyvodic et al. described a system like this that both controls the tasks being performed by a subject, and allows for real time monitoring of the data to make sure that they are reasonable. However, critically, the approaches used at the time, such as Voyvodic's, didn't "close the feedback loop": They did not show that one can use the information taken from the brain using fMRI as the basis of meaningfully guiding the cognitive tasks of a subject, or training a subject to control their brain activation or to impact behavior or disease. The notion that you can measure brain activation and the notion that you can control behavior does not make clear, for all the reasons stated above, exactly how or whether one could use fMRI information specifically to guide the cognitive processes of a subject.

Fourth, it was not obvious whether the hemodynamic delay inherent in the brain's blood flow signals would make guiding the cognitive processes of a subject using fMRI impossible. There is an inherent biological delay of about 3-5 seconds from the time of neural activation to the time that the fMRI signal shows a meaningful increase (as opposed to the delay from the time of measurement of the fMRI signal to the time of providing the subject information from this signal, which can be shorter). Given that cognitive training signals are ideally closely time-locked, it was therefore not obvious whether an fMRI signal could be meaningfully used to train subjects or guide their cognitive tasks. It could have simply been confusing to them given this length of delay.

Fifth, it was not obvious whether the information being provided to subjects would be meaningful to them in guiding their cognitive processes, since it was possible that fMRI might provide no further guidance beyond simple introspection.

For example, there are now data demonstrating that both healthy subjects and chronic pain patients can learn to control their cognitive processes in order to decrease perceived pain using information from fMRI. This is a surprising result, which is part of why it was prominently published. Pain patients already have excellent "feedback" of their level of pain based upon their introspection of how much the pain hurts. It would seem intuitive that they could learn to control their cognitive processes using the pain signal itself. It is actually quite surprising that showing subjects information from inside their own brain, i.e., information already known to be closely corresponding with their own pain, can be used to meaningfully train them to guide their cognitive processes and control their pain beyond cognitive training methods that do not use fMRI feedback information, which has now been shown in a number of control groups.

Finally, I was first made aware of the possibility of using fMRI as the basis for guiding cognitive processes, and potentially having an impact on disease, when Christopher deCharms suggested the possibility of experiments to test this idea, and asked if I would be interested in collaborating and performing work on this topic within my research group. As a historical aside, while I was supportive of this interesting idea at the time and interested in pursuing it, I cautioned Dr. de Charms that this was, in my opinion, a high risk project that could easily fail for any of a number of technical and conceptual reasons. Based on my contribution to this work, I was named as a co-author on papers entitled:

> deCharms, C.R., Christoff, K., Glover, G.H., Pauly, J.M., Whitfield, S., and Gabrieli, J.D.E. (2004) Learned regulation of spatially localized brain activation using real-time fMRI. NeuroImage, 21, 436-443.
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> deCharms, C.R., Maeda, F., Glover, G.H., Ludlow, D., Pauly, J.M., Soneji, D., Gabrieli, J.D.E., and Mackey, S.C. (2005) Control over brain activation and pain learned using Real Time fMRI. Proceedings of the National Academy of Sciences of the United States of America, 102, 18626-18631.

For all of these reasons, it is my opinion that at the time this application was originally filed, it was not at all obvious whether one could successfully train subjects to control brain activity or to guide their cognitive tasks based upon information derived from fMRI, or exactly how one would go about doing it given the large number of potential methods and available techniques.

I, John Gabrieli, further declare that all statements made herein are true to the best of my knowledge, or if made upon information and belief, are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 7/17/07 By: _____
John Gabrieli, Ph.D.